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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/605,452 | 09/30/2003 | William G. Kerr | 1372.79.PRC | 2451 |

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| EXAMINER | |
|---|---|
| HAMA, JOANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/605,452 | KERR ET AL. | |
| | Examiner | Art Unit | |
| | Joanne Hama, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-23 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *none*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application was filed September 30, 2003 and claims priority to U.S. Provisional Application 60/319,583, filed September 30, 2002.

Claims 1-28 are pending.

### *Election/Restrictions*

Applicant's election without traverse of Group V (claims 18, 19, 24-27) in the reply filed on October 28, 2004 is acknowledged.

Claims 1-17, 20-23, 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 28, 2004.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 19, 24-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With respect to claims 18 and 19, while the specification teaches that s-SHIP expression is decreased after electroporation of embryonic stem cells with anti-SHIP shRNA (paragraph 71, see also Figure 8), nothing in the specification teaches one skilled in the art how to make shRNA that targets SHIP RNA. While many researchers have been successful in making and using shRNA, the art shows that the design of molecules that target mRNA is empirical. Jen et al. (2000, Stem Cells 18:307-319) teach some of the problems that researchers face when administering polynucleotides to a cell. When one skilled in the art needs to design a targeting molecule, s/he keeps in mind some major potential problems of antisense experiments. These include mRNA site selection, delivery, and localization. In terms of mRNA site selection, one must design a molecule that will attach to a single strand of mRNA. In the cell, transcripts exist in low energy conformations in which secondary structures dominate in folding the linear polymer. Furthermore, transcripts interact with cytoplasmic proteins and produce further structural properties (page 313, section headed "mRNA site selection"). In terms of delivery, naked oligonucleotides are poorly incorporated into cells. Thus, in cell culture, many classes of compounds have been used as delivery vehicles include cataionic liposomes, cationic porphyrins, fusogenic peptides, and artificial virosomes (page 313, section headed "Delivery"). In the case of localization, the polynucleotide needs to make its way to the appropriate intracellular compartment as its target mRNA. Intracellular trafficking seems to play an important role in the fate of these molecules since their spatial distribution does not correspond to simple diffusion. Many factors determine

localization patterns of polynucleotides including the antisense agent itself, delivery vehicle, and targeted cell type. In addition, evidence for cell cycle-dependent localization patterns has been reported with nuclear localization predominantly in the G2/M phase (page 314, section headed "Localization"). Even after making the molecule, one must then test the molecule as sometimes, the molecule has unexpected effects on the cell and will skew the results. While it seems apparent that the Applicants were able to design an anti-SHIP molecule (Figure 8), nothing in the specification teaches one how to make it.

While the Applicants were able to administer shRNA that targets SHIP in embryonic stem cells, nothing in the specification teaches the steps needed to manipulate these stems cells to proliferate and differentiate. According to the art, there does not appear to be a resounding consensus as to what biological function(s) SHIP has in a variety of hematopoietic and differentiated cell lines. To date, one major way that SHIP is thought to play a role in cell proliferation is by activation of the MAPK pathway. It is thought that interaction of SHIP with Grb2 would localize the factors needed for the cascade of events leading to MAPK activation. However, work by Okada et al. (1998, Journal of Immunology, 161: 5129-5132) teach that SHIP-deficient DT40 cells activate MAPK to almost the same level as that seen in wild type DT40 cells, suggesting that the MAPK pathway appears to be independent of SHIP (page 5131, first column, first full paragraph; see also Figure 3). One might argue that DT40 cells are cells that have differentiated into B-cells and are not developmentally comparable to a hematopoietic cell. If this is the case, then the specification needs to be taught

what characteristics of the DT40 cells make it undergo a different mechanism that enable it to proliferate differently from a hematopoietic cell.

Work by Liu et al. (1997, JBC; 272: 8983-8988), teaches the use of two SHIP constructs without a functional SH2 domain. In this study, Liu et al show that wild type (WT)-SHIP and SHIP with a loss-of-function in the SH2 domain has no apparent role in cell proliferation. This suggests that there should be no reason to imply that the use of shRNA to target any SHIP affects cell proliferation. The first SHIP SH2 mutant (Δ-SH2-SHIP) lacks the second half of the SH2 domain, corresponding to amino acids 44-149 of the full length SHIP. The second SHIP construct (R34G-SHIP) is a point mutant wherein the critical arginine in the FLVR sequence was replaced by a glycine (page 8984, first column, second paragraph). Functionally, it would seem that these constructs are similar to s-SHIP described by the Applicants (specification, paragraph 50). In one study, Liu et al. took DA-ER (murine hematopoietic cell line) cells that were infected with a construct that expressed HA-tagged WT-SHIP and parental cells not infected with construct and compared their rate of growth. Each day, trypan blue was used to monitor cell viability. What was found that while all cells had similar growth rate in suspension, at confluence on the third day, there was more death in cells that expressed WT-SHIP. In their next experiment, Liu et al. overexpressed HA-WT-SHIP, HA-Δ-SH2-SHIP, HA-R34G-SHIP and grew them in suspension. On the third day, after confluence was reached, cells that expressed WT cells were much less viable than cells that expressed the dominant negative form of SHIP or cells that were grown from the parental line

that did not express SHIP from a construct (page 8987, first column, fourth paragraph, see Figure 4B). Liu et al. also showed that WT-SHIP-induced loss of viability was mediated by apoptosis (page 8987, first column, fifth paragraph to second column, first paragraph; see also Figure 4C). Based on these results, while Liu et al.'s study demonstrates that overexpression of WT-SHIP increases the incidence of apoptosis, their results do not demonstrate that SHIP having a mutation in the SH2 domain has any obvious biological effects cell growth or apoptosis in DA-ER cells. That said, nothing in the art or the specification teaches that a SHIP2 with a loss-of-function mutation in the SH2 domain would predictably or necessarily have a role in cell proliferation. For that matter, nothing in the art or specification predicts or indicates that designing an shRNA that targets s-SHIP or any SHIP would necessarily have an effect on cell proliferation.

According to work by Helgason, et al. (1998, Genes and Development, 12: 1610-1620), a targeted disruption in exon 1 of the SHIP gene resulted in mice that had hemapoietic perturbations, lung pathology, and a shortened life span. In particular for the hemapoietic perturbations, peripheral blood smears revealed a substantial increase in the percentage of circulating monocytes and mature neutrophils with a concomitant decrease in the percentage of circulating lymphocytes. Cytospins of bone marrow from SHIP-/- mice showed a similar increase in mature neutrophils, with a reduction in lymphoid and late erythroid cells (page 1612 first and second column to page 1613, first column, first paragraph). While these results appear to contradict claims 18, 19, 24-27 in that

loss of SHIP appears to reduce the number of lymphoid and late erythroid cells, the Applicants point out in their specification that the mutation strategy employed by this group only targets the full length form of SHIP and does not target the embryonic form, s-SHIP, which initiates transcription from a promoter located 3' of the first exon. Thus, the s-SHIP isoform in the embryo or in hematopoietic stem cells should not be affected. However, according to the specification, in preliminary experiments, the inventors were unable to detect s-SHIP protein expression from total bone marrow of adult mice in which the first exon of SHIP was insertionally mutated. If it could be shown that s-SHIP expression is unaffected in these mice, then a novel phenotype could be predicted for s-SHIP and SHIP null mice (specification, paragraph 72). However, at the time of filing, it is unclear if there really was s-SHIP. Based on what has been shown in the art and the results presented by the Applicants, it is unclear what the role for s-SHIP is in hemapoietic stem cells and embryonic stem cells. There is no guidance given by the art or the specification to predict that SHIP has a role in controlling proliferation and/or differentiation in hemapoietic stem cells and embryonic stem cells.

At the time the Application was filed, nothing in the specification or the art teaches a method wherein the loss of SHIP in hematopoietic progenitors of mature blood cell, hemapoietic progenitors of lymph cells, and embryonic stem progenitors would predictably and reliably result in cell proliferation and differentiation. Nothing in the specification or the art teaches how to manipulate SHIP to induce proliferation. Furthermore, nothing in the specification or the art

teaches how to induce differentiation. Thus, it is unclear how the use of a dominant negative (claims 24-27) in hematopoietic progenitors of mature blood cell, hemapoietic progenitors of lymph cells, and embryonic stem progenitor cells would result in the differentiation. Thus, unless there is a reduction to practice, the Applicants have not enabled one skilled in the art a method to take hematopoietic progenitors of mature blood cell, hemapoietic progenitors of lymph cells, and embryonic stem progenitors and manipulate them to proliferate and differentiate.

Claims 18, 19, 24-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does

not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification teaches an shRNA against SHIP was electroporated into embryonic stem cells and reduced s-SHIP expression (Example 8), the art shows that the method of expressing any shRNA to block expression of a gene is not reliable and thus not predictable. For this reason, the use of shRNA needs to be shown empirically that it functions specifically in the cell and the sequence of the shRNA must be disclosed. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the Applicant demonstrated that an shRNA construct was used to reduce s-SHIP expression. As discussed earlier in the Enablement section, not all shRNA molecules reliably inhibit target genes. For this reason, when the situation arises that a construct specifically targets RNA, the sequence of it needs to be disclosed. Further, the specification has not described predictable ways to generate any shRNA encompassed by the claims beyond the one shown in Example 8. Characterization is not adequate if one supplies a

nucleotide sequence or a protein sequence or demonstrates that a construct works without disclosing its sequence. The skilled artisan cannot envision a sequence of shRNA targeting s-SHIP from a result wherein the expression of s-SHIP expression is reduced. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no shRNA meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated:

In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can

distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Because Applicants have failed to provide an adequate written description of the materials used in the compositions and methods claimed and because there is no evidence that Applicants possessed any shRNA beyond that disclosed and/or known in the prior art, the rejected claims fail to meet the written description requirement under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is (571) 272-2911. The examiner can normally be reached on Monday-Friday 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JH

Jon Weber
AU1632